Early Initiation of Anti-TNF is Associated with Favourable Long-term Outcome in Crohn's Disease: 10-Year-Follow-up Data from the Swiss IBD Cohort Study

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Abstract: BACKGROUND AND AIMS The optimal timing of treatment escalation in Crohn's disease [CD] remains a challenging issue, and very little is known about its long-term development following early versus late administration of anti-TNF antibodies. The long-term outcome of Swiss CD patients was comparatively assessed in an up to 10-year follow-up, using patients participating in the Swiss Inflammatory Bowel Disease Cohort Study [SIBDCS]. METHODS Prospectively collected SIBDCS patient data, including disease history, baseline characteristics at enrolment, and course of disease, were analysed in patients with early versus late [<24 versus 24 months after diagnosis] and no anti-TNF treatment. RESULTS A reduced risk of developing bowel stenosis was found in patients who received early anti-TNF treatment. This association was seen in patients overall and also in the subgroups of CD patients without pre-existing complications [Log-rank test: $p < 0.001$].Furthermore, osteoporosis and anaemia were observed significantly less frequently in patients who received early anti-TNF treatment, compared with either patients who received treatment late [$p < 0.001$ and $p = 0.046$, respectively] or were never [$p < 0.001$ for both] treated with anti-TNF antibodies. Patients with early anti-TNF administration sought medical consultations significantly less often, including gastroenterologists in private practice [$p = 0.017$], ambulatory [outpatient] hospital visits [$p = 0.038$], and a composite of any medical visits [$p = 0.001$]. The percentage of patients unable to work was lowest for early-anti-TNF-treated patients, in comparison with patients who were treated late or never [3.6% vs 8.8% vs 3.7%, $p = 0.016$]. CONCLUSIONS In CD patients within the SIBDCS, early anti-TNF administration was found to be associated with several indicators of a more favourable long-term outcome.

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EARLY INITIATION OF ANTI-TNF IS ASSOCIATED WITH FAVOURABLE LONG-TERM OUTCOME IN CROHN'S DISEASE: 10-YEAR-FOLLOW-UP DATA FROM THE SWISS IBD COHORT STUDY

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Abstract

Background and Aims

The optimal timing of treatment escalation in Crohn's disease (CD) remains a challenge and very little is known on the long-term evolution in early versus late administration of anti-TNF antibodies. We comparatively assessed the long-term outcome in Swiss CD patients with an up to 10-year follow-up using patients participating in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS).

Methods

Prospectively-collected SIBDCS patient data, including disease history, baseline characteristics at enrolment and course of disease were analysed in patients with early versus late (<24 versus >=24 months after diagnosis) and no anti-TNF treatment.

Results

We found a reduced risk of developing bowel stenosis in early anti-TNF treated patients. This association was seen in patients overall and in the subgroups of CD patients without pre-existing complications (Log-rank test: $p<0.001$).

Further, osteoporosis and anaemia were observed significantly less frequently in early anti-TNF treated patients, compared to both, patients late ($p<0.001$ and $p=0.046$, respectively) or never ($p<0.001$ for both) treated with anti-TNF antibodies. Patients with early anti-TNF administration were significantly less often seeking medical consultation, including a gastroenterologist in private practice ($p=0.017$), ambulatory (outpatient) hospital visits ($p=0.038$) and a composite of any medical visits ($p=0.001$). Percentages of patients unable to work during the last 3 months were lowest in early anti-TNF treated patients in comparison to patients who were treated late or never with anti-TNF agents (3.6% versus 8.8% versus 3.7%, $p=0.016$).

Conclusions

We identified early anti-TNF administration to be associated with several indicators of a more favourable long-term outcome in CD patients within the SIBDCS.

Key words

anti-TNF, early intervention, long-term outcome

Introduction

The optimal management of patients suffering from chronic inflammatory illnesses like Crohn's disease (CD) has not been clarified and remains a matter of ongoing research. A major challenge lies in the prediction of the future disease course which is difficult or even impossible, according to the tools currently available in clinical practice [1].

An important breakthrough in CD therapy however was the approval of anti-tumor necrosis factor (TNF) drugs in 1998 [2].

The substantial value of anti-TNF drugs was soon realized and new possibilities of disease control seemed achievable. Strong anti-inflammatory activity of TNF inhibitors enabled a 'treating patients to target' approach, aiming at complete control of inflammation beyond mere symptom surveillance and clinical remission [3]. Even in the nearer future individualised therapies might be state of the art. A potentially beneficial impact of anti-TNF drugs on the evolution of disease course was indicated in animal [4] as well as cohort studies in humans [5-7].

Besides that, several studies have compared a 'step-up' with a 'top-down' treatment strategy in CD [8-10]. Current literature favours a 'rapid step-up' strategy with stepwise early introduction of immunosuppressive agents (IM) and timely addition of anti-TNF [11-14], although the benefit of early IM remains controversial [13, 15]. The impact of a 'top-down' strategy with early introduction of anti-TNF has been investigated by even more studies [4, 16-25], including the key question, whether the disease course may be modified through early anti-TNF administration [4].

However, the evidence of a potentially beneficial impact on the disease course and our knowledge on proper selection of patients in need of an early aggressive treatment remains limited. Specifically, the long-term evolution of disease beyond the usual observation periods of one year in most studies and 5 years in very few instances remains unknown.

Using the prospectively obtained data from patients participating in the SIBDCS we aimed to investigate, if early anti-TNF administration, defined as initiation during the first 24 months after CD diagnosis, is associated with beneficial effects on predefined outcome parameters in CD, compared to either patients with initiation of anti-TNF beyond the first 24 months since diagnosis or without anti-TNF treatment.

Materials and Methods

Study Population:

In 2006 the nationwide inclusion of IBD patients into the SIBDCS started. The SIBDCS was designed as a prospective cohort study. At enrolment, all patients provided written informed consent for participation in the study. SIBDCS receives ongoing supporting grants from the Swiss National Science Foundation (SNSF) and has been approved by the local ethical committees of all participating centres. SIBDCS has been described in detail by Pittet et al. [26, 27].

At time of inclusion, patients as well as the treating physicians filled out enrolment questionnaires. Patient questionnaires covered questions about the individual perception of the clinical disease course, the severity of symptoms as well as quality of life (QoL) and socioeconomic associations. Physicians questionnaires focused on clinical characteristics, classification and course of IBD. Patients as well as treating physicians are followed up annually by follow-up (fu) questionnaires similar to the original inclusion questionnaires. Data of all CD patients enrolled into SIBDCS since its start in 2006 have been used for the analysis of our study. Data extraction from the SIBDCS data base as well as the following statistical analysis were performed by the SIBDCS data centre in Lausanne, Switzerland.

Data extractions, definitions:

All data were collected prospectively through the SIBDCS cohort study and analysed retrospectively at the cut-off date 12/31/2016 for our study. Anti-TNF medication was defined as an administration of at least one dose of the three anti-TNF agents currently approved for treatment of CD in Switzerland, i.e. infliximab, adalimumab or certolizumab pegol during the observation period.

To assess the impact of timing of anti-TNF administration on the disease course, we defined three groups: 'early anti-TNF', i.e. patients having received anti-TNF within the first 24 months since diagnosis; 'late anti-TNF', i.e. patients having received anti-TNF medication after 24 months since diagnosis and 'no anti-TNF', i.e. patients who have never received anti-TNF therapy since IBD diagnosis within the observation time.

Primary outcomes of our study included bowel stenosis, perianal fistula, other fistula, any fistula, perianal surgery, intestinal surgery, any surgery and extraintestinal manifestations (EIM). These outcome parameters were analysed using the log-rank test

looking at time to first complication. 'Secondary outcomes included the occurrence of osteoporosis and anaemia, utilization of health care resources and inability to work because of CD (absence from work due to other reasons was not included in these analysis). Within secondary outcomes the rates of occurrence between different treatment groups were compared.

Safety data included rates and differences in occurrence of colorectal cancer (CRC), intestinal lymphomas (IL) and deaths. Additionally, the rates of opportunistic infections which led to anti-TNF therapy cessation were also assessed.

In the survival analysis of the primary outcomes, patients who were treated early (<24 months), were compared with patients who were treated late (>=24 months) with anti-TNF agents. Pre-existing complications were defined as any single or more of the same complications, which were analysed as primary outcomes during follow-up after anti-TNF induction, existing already prior to anti-TNF induction.

To define bowel stenosis, there is a lack of standardized definitions, which has been aimed at overcoming by a very recent expert consensus, according to which the best current definition for a small bowel stricture is based on a combination of wall thickening, luminal narrowing and pre-stenotic dilation [28]. Assessing these parameters, the diagnosis of bowel stenosis in our study was derived by the examination of clinical symptoms and signs, radiological examinations and endoscopy.

'Perianal fistula' refers to any kind of fistula located in the perianal area, such as submucosal, intersphincteric, transsphincteric, suprasphincteric or extrasphincteric fistulas. 'Other fistula' refers to any kind of non-perianal fistula, whereas 'any fistula' combines perianal as well as any kind of non-perianal fistula. Likewise, 'perianal surgery' refers to perianal surgical procedures, such as drainage of perianal abscesses, seton-placement or any form of fistula extraction/closure procedure, whereas 'intestinal surgery' refers to any kind of surgery performed at the intestine related to CD, including any kind of resection or ostomy surgery. Again 'any surgery' refers to the need for any surgery in relation to CD, irrespective of location or type of procedure.

EIM includes peripheral arthritis/arthralgia, uveitis/iritis, pyoderma gangrenosum, erythema nodosum, aphthous oral ulcers/stomatitis, ankylosing spondylitis (Bechterew), sacroiliitis and primary sclerosing cholangitis.

In terms of complications we assessed osteoporosis and anaemia due to their clinical relevance.

Further, we tested for differences in the utilization of health care resources across treatment groups. We therefore assessed medical visits related to CD at general practitioners, gastroenterologists in private practice, ambulatory visits at hospitals and hospitalizations. The category 'other' includes medical visits at any physician not falling into the predefined categories above, for example specialised surgeons like coloproctologists. With every patient questionnaire, the data on utilization of health care resources was collected regarding the respective last 3 months of each annual follow-up questionnaire. The recall period of 3 months was chosen in cooperation with experts in public health and psychologists, which were involved in the SIBDCS from the very beginning until now. By using a longer recall period however, the risk of recall bias and inadequate data considerably increases.

Similar to the data on utilization of health care resources, data on work ability was also assessed with every annual patient questionnaire regarding the last 3 months since the last follow-up patient questionnaire within the cohort.

Statistical Analysis

All statistical analyses were carried out using the Stata Software (v. 14.2, StataCorp, College Station, TX, USA).

Categorical data were summarized as raw frequencies and relative percentages. Differences in categorical data distribution between two or more independent groups were assessed using the chi-squared test, or the Fisher's exact test in case of low sample size.

Continuous data distribution was assessed using normal quantile-quantile (QQ)-plots. Gaussian distributed data were summarized as mean, standard deviation (SD) and range, while non-Gaussian distributed data were summarized as median, interquartile range (IQR) and range. Differences in means for Gaussian distributed data between two independent groups were assessed using the Student's t-test, or ANOVA for more than two independent groups. Differences in distribution for non-Gaussian distributed data between two independent groups were assessed using the Wilcoxon-Mann-Whitney rank sum test, or the Kruskall-Wallis test for more than two groups.

The primary outcomes were analysed as time-to-event data. Complication-free proportions according to time were derived using Kaplan-Meyer survival estimator. The

192 log-rank test was used to assess overall differences between survival curves for
193 independent groups.
194 A p-value <= 0.05 was considered as statistically significant.
195

Results

Study population

Within the ten-year timespan from the start of patients' inclusion into SIBDCS in early 2006 until the 31st of December 2016 a total of 1707 adult CD patients were enrolled and 1592 patients could be analysed (Figure 1). Demographic data and clinical characteristics of the study population are shown in Table 1.

Of note, patients with early anti-TNF therapy had a younger age (median age 32 years vs. 44 years and 48 years, in late and no anti-TNF, respectively, $p< 0.001$) and shorter disease duration at the time of inclusion into our study, with a higher fraction of B1p phenotype.

Looking at complications, patients without a given pre-existing complication prior to anti-TNF induction had a younger age, shorter disease duration and lower rate of other complications compared to their counterparts with the respective pre-existing complication.

Regarding perianal surgery however, there was no significant difference in age between patients with or without perianal surgery prior to anti-TNF induction ($p=0.067$). Also, there were no significant differences in the presence of complications other than EIM between patients with or without EIM manifestation prior to anti-TNF induction ($p=0.084$).

Disease course and complications

Bowel stenosis

We found a reduced risk of developing stenosis in early anti-TNF treated patients compared to late anti-TNF treated patients, using Kaplan-Meier analysis as shown in Figure 2 (log-rank test: $p<0.001$). This difference was most pronounced in the subgroups of CD patients without pre-existing complication (log-rank test: $p<0.001$), whilst only by trend in patients with pre-existing complication ($p=0.147$, Table 2). A significant difference between early and late anti-TNF treated patients was also detected without considering pre-existing complications ($p<0.001$, Supplementary Table 1).

Amongst patients without pre-existing complication of bowel stenosis a larger number of early anti-TNF treated patients were free from bowel stenosis 2, 5 and 10 years after anti-TNF initiation (95.1%, 83.6% and 67.8%, respectively), than late anti-TNF treated patients (88.1%, 68.2% and 45.7%, Supplementary Table 2).

Penetrating complications and surgery

Although we observed a global difference in need of perianal surgery across the patient groups overall (p=0.002, Table 2), this difference was predominantly seen between patients with versus without pre-existing complication and not according to early versus late anti-TNF treatment (Supplementary Figure 1).

In addition, there were no significant differences favouring early intervention neither regarding intestinal or perianal surgery nor occurrence of perianal fistula or fistula overall (Table 2).

Amongst patients without pre-existing complication of any penetrating complication or surgery a larger number of early anti-TNF treated patients were free from penetrating complications and surgeries 10 years after anti-TNF initiation (60.1%, 68.2%, 70.8% and 83.4%, respectively), than late anti-TNF treated patients (50.7%, 63.6%, 57.2% and 75.6%, Supplementary Table 2).

Extraintestinal manifestations

We observed no difference in the development of EIM in early versus late anti-TNF treated patients without pre-existing complication (Supplementary Figure 2). However, early treated patients with pre-existing complication appeared to develop less EIM by trend (p=0.087, Table 2).

Looking at pre-existing complication of EIM a larger number of early anti-TNF treated patients were free from EIM 2, 5 and 10 years after anti-TNF initiation (75.0%, 49.8% and 26.3%, respectively) than late anti-TNF treated patients (74.7%, 46.8% and 22.1%, Supplementary Table 2).

Osteoporosis and anaemia

Osteoporosis and anaemia were observed significantly less frequently in early versus late anti-TNF treated patients (p<0.001 and p=0.046, respectively, Supplementary Table 3, Figure 3).

Medical consultations and hospitalizations

Patients with early anti-TNF administration were significantly less often in need for medical consultations, including consultations with a gastroenterologist in private practising (p=0.017), ambulatory hospital visits (p=0.038) and a composite of any

medical visits at all (p=0.001). There was, however, no difference in visits to a general practitioner or any other CD related medical visits.

Overall hospitalizations between the three tested groups differed with the lowest number of hospitalizations in the group of patients never treated with anti-TNF (p=0.001, Supplementary Table 4). However, there was no difference between patients with early vs. late anti-TNF administration (Figure 4) regarding hospitalization rates.

Absence from work

TNF treatment influenced work disability due to CD across all treatment groups (p=0.016, Supplementary Table 5). Early treated patients were by trend less likely to be unable to work with 3.6% of patients absent from work compared to 8.8% in late treated patients (p=0.096, Supplementary Table 5, Figure 5).

Safety

There were no significant differences in CRC or IL between the three different treatment groups (Supplementary Table 6). The absolute number of patients observed regarding opportunistic infection leading to therapy cessation was very low with 1 patient (0.4%) within the early and 4 patients (0.6%) within the late treatment group (Supplementary Figure 3).

Discussion

In this study we demonstrated an association of early anti-TNF administration with reduced risk of developing bowel stenosis. In addition, patients with any pre-existing complication were relatively protected from a recurrence of this respective outcome 5 and 10 years after early vs. late anti-TNF initiation.

Specifically, osteoporosis and anaemia were less frequently observed in the group of patients with early anti-TNF treatment. Furthermore, patients with early anti-TNF administration were less frequently seeking medical consultation and by trend showed lower rates of absence from work due to CD compared to patients with late anti-TNF administration.

In terms of stricturing disease behaviour, our findings are in line with a previous study from SIBDCS, where a significant association between IM or anti-TNF agents and reduced bowel stenosis was observed [16].

Besides such a preventive effect, anti-TNF agents might also be effective in patients with established fibrotic disease. This has previously been suggested in a study by Allocca et al. [29] in stricturing CD, showing that anti-TNF agents may prevent surgery in up to two-thirds of patients with intestinal stenosis. Beneficial effects of early anti-TNF administration seem to be selective for bowel stenosis since our study and previous investigations did not identify any effects on the overall need for surgery in CD [30-32].

The reason for stricturing disease to be more prone to be modulated by early anti-TNF administration in our study as compared to penetrating disease remains both unclear and also controversial. Some of recently published other studies on this topic also indicated the opposite, showing that anti-TNF therapy might prevent the development of penetrating (B3) but not stricturing (B2) disease migration [33-35].

A possible explanation for our findings might be that bowel stenosis and scar tissue formation reflect the result of a long-term cumulative effect of continuous inflammation. Stopping or attenuation of inflammation at an early stage might therefore prevent the ongoing progression of scar tissue formation, wall thickening, luminal narrowing and thus evolution of stenosis over time [36-38]. In contrast, penetrating disease might manifest more suddenly at any time of the disease course [39], turning it out to be less susceptible to modification by early anti-TNF treatment.

According to our results, the overall need for surgery doesn't seem to be affected by the time point of anti-TNF intervention. This is in line with previous studies [40], indicating

317 that an early use of anti-TNF can positively affect symptoms of stenosis but might not yet
318 be, even though risk factors can be identified[41], an appropriate strategy to reduce
319 surgical interventions [31, 32, 42, 43].
320 In contrast to this, a retrospective analysis among Korean CD patients found significantly
321 longer times to intestinal surgery ($p< 0.001$), stricturing complications ($p= 0.002$), and
322 penetrating complications ($p< 0.001$) in the early anti-TNF/ IM groups compared to the
323 late treatment group (47).
324 The development of EIM does not seem to be affected by the point of time of anti-TNF
325 administration. Also, pre-existing EIM does not seem to be affected differently by early or
326 late anti-TNF intervention.
327 There are, however, studies on EIM and IBD phenotypes and medication also including
328 studies within the SIBDCS indicating that the presence of EIM is often associated with
329 active disease, positive family history or treatment strategy (higher AZA exposure) [44,
330 45]. Nonetheless, to the best of our knowledge there are no studies addressing the best
331 point of time of anti-TNF administration regarding evolution of EIM.
332 In our study early anti-TNF administration was associated with a lower risk of
333 osteoporosis which remains a frequent problem in IBD patients [46]. Previously,
334 infliximab therapy has been associated with increased biochemical markers of bone
335 formation without increasing bone resorption [47]. Whether this may be due to a direct
336 beneficial effect of TNF blockade on bone turnover, a beneficial effect on CD activity
337 resulting in decreased glucocorticoid exposure or both remains difficult to determine,
338 even more so as osteoporosis was not the primary outcome of this study.
339 We found early anti-TNF administration to be associated with a lower risk of anaemia.
340 Short-term anti-TNF therapy may significantly improve iron metabolism and,
341 subsequently, anaemia in IBD [48]. This effect appears to be primarily related to the
342 modulation of the cytokine network, leading to a relevant decrease of hepcidin, a master
343 regulator of anaemia of chronic disease. On the other hand, during long-term treatment
344 anti-TNF therapy might also improve iron deficiency anaemia through the induction of
345 mucosal healing.
346 We identified a lower need for consultations at gastroenterologists in private practice and
347 outpatient visits at hospitals in the early treatment group but not in hospitalization rates
348 and consultations of general practitioners. In a systemic review [49] assessing reduction
349 of hospitalization rates as well as surgery rates through immunosuppressive therapy,

anti-TNF agents reduced the odds of hospitalization by half. Even more encouraging are the results of another investigation, revealing an association of timely anti-TNF administration and decrease in hospitalization rates [20].

There are only few studies investigating absence from work due to CD in relation to medical therapy [50-55] and to the best of our knowledge, no study so far addressed effects of timing of anti-TNF on CD-related work disability. We showed significantly lower rates of absence from work amongst early anti-TNF treated CD patients compared to late treated patients and even slightly lower rates of work disability compared to patients never having been treated with anti-TNF.

With the increase in availability of newer agents to treat IBD, the question of positioning and determination of the best timepoint in the course of the individual patient's disease is getting more imminent. Beyond anti-TNF a multicentre open-label phase IV trial (LOVE-CD; NCT02646683) is currently recruiting patients with CD, aiming to investigate whether clinical and endoscopic remission at week 26 (1°EP) is different between patients with early (<24months after diagnosis) vs. late primary administration of vedolizumab. Similar studies also looking at complications rates are desirable for other newer agents, including ustekinumab and JAK-inhibitors.

Our study has several strengths and limitations. As a limitation, CD patients from tertiary care hospitals are over-represented within SIBDCS and the patient population of the SIBDCS cannot be considered fully population-based with a presumable preponderance of patients with more severe disease. Moreover, data acquired by questionnaires may be linked with a risk of bias, above all reporting and recall biases. Further, there are no detailed data available on individual doses and time intervals of anti-TNF administration. The patient numbers in some of our analysed subgroups remain rather small. This specifically applies for patients with early anti-TNF intervention and pre-existing complication of the respective outcome parameter. Nevertheless, those patient groups were still kept in the analysis as we think they provide interesting information. Overall, we must underline that our investigation may not be sufficiently powered to draw any robust conclusions with regards to the risk benefit balance of early anti-TNF administration. In terms of risks, severe adverse events (e.g. major infections requiring ICU or melanoma) have a tremendous impact but are fortunately infrequent. Due to the latter, larger study population or large (multinational) patient registries are advantageous. In addition, all our findings represent associations and we can only

speculate about underlying causes and effects. For definite answers, prospective randomized long-term studies would be needed. However, such trials are virtually impossible to perform. Therefore, prospective cohort studies are adequate means to address the potential impact of early anti-TNF administration on the course of disease and the rigorous annual follow-up with detailed physician and patient questionnaires represent a strength of our study. In addition, the long prospective follow-up period of up to 10 years represents another important strength.

Furthermore, our study may even have underestimated the benefit of early anti-TNF administration since patients in the no anti-TNF group might be positively selected for a less severe disease course (as indicated by several outcome parameters with apparent beneficial results in this group including Crohn's Disease Activity Index (CDAI) score, rates of hospitalization, perianal fistula formation and perianal surgery). In view of this, the reduction of bowel stenosis, lower rates of osteoporosis and anaemia, absence from work due to CD and ambulatory hospital visits in the early treatment group shown by our study indicate a true beneficial effect.

Importantly, one of the biggest risk factors for the development of any complication appeared to be a prior history of the very same complication. Considering this factor, we compared patients with or without a history of the respective complication separately in our survival analysis to distinguish the different preconditions in time to event.

In conclusion, we observed an association between early anti-TNF administration and several beneficial clinical outcomes in CD, including a reduced risk of bowel stenosis, osteoporosis and anaemia. Additionally, we observed lower rates of medical consultations and absence from work due to CD upon early anti-TNF treatment. Accordingly, patients with a stricturing type (B2) or at risk to develop such a phenotype (i.e. those with long-segment or multi-segmental small bowel inflammatory lesions) might benefit most from an early anti-TNF intervention. Our results thus highlight the importance of a proper identification of patients in need of early anti-TNF administration, which currently remains a big challenge for the practicing clinician in the absence of high-accuracy tools to predict future course of CD.

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Conflict of interest

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Authors' Contributions

RF, LB, NF, and GR formed the concept of the study. NF, LB, RF and GR performed pre-evaluations for data extraction from the SIBDCS. LB, BMI, and RF carried out first analyses of data. NF, RF and LB performed the final statistical analysis. RF drafted the manuscript. LB, RF, NF and GR wrote the manuscript. RF, LB, NF, GR, JZ, MS, BM, TG, PS, BM, ES, AS and SV read the final manuscript, gave critical input, and approved the final manuscript.

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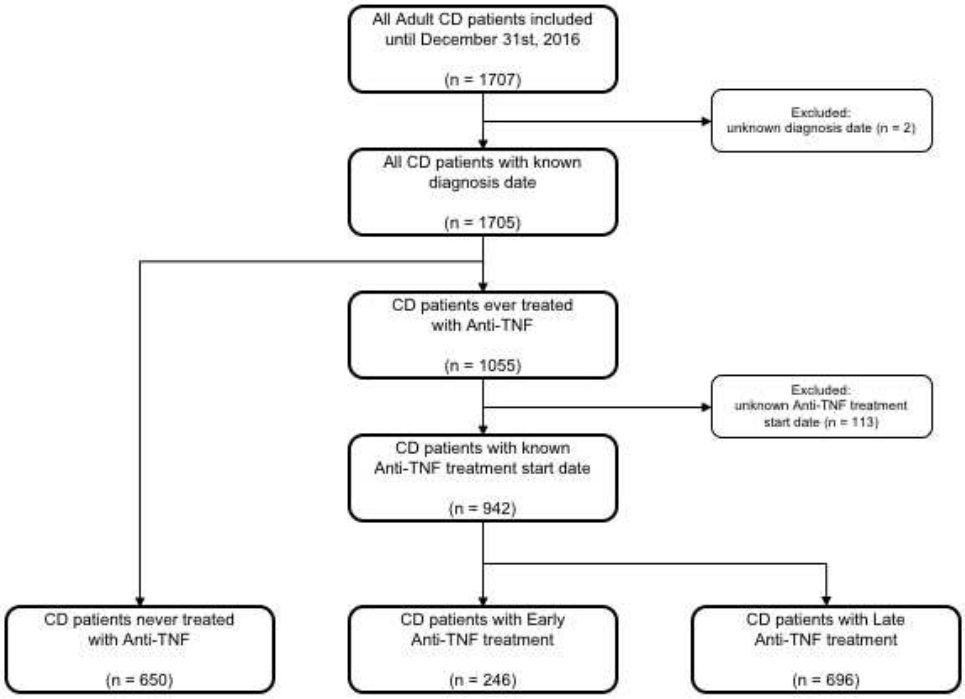
610 **Figures and Tables**

611

612 ***Figures***



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614 Figure 1: Flowchart Study Population

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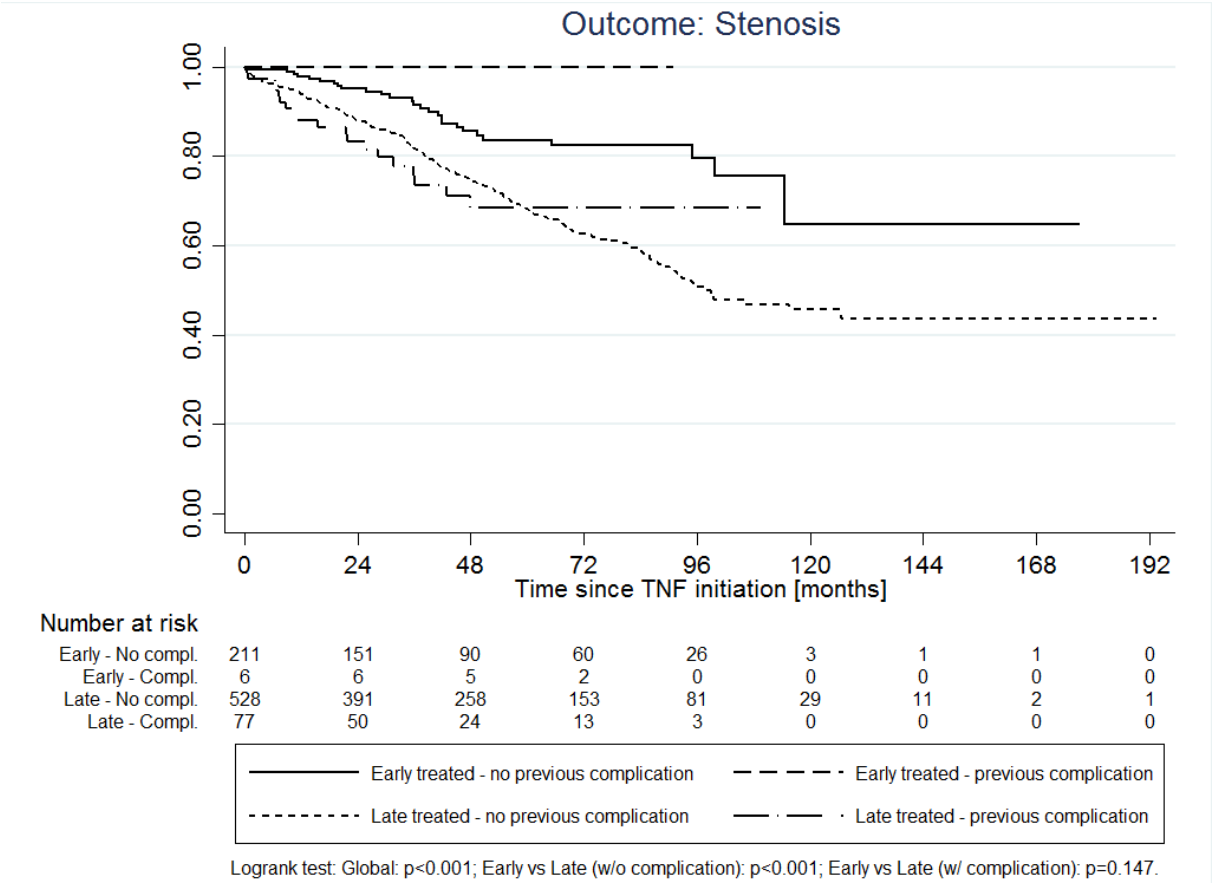
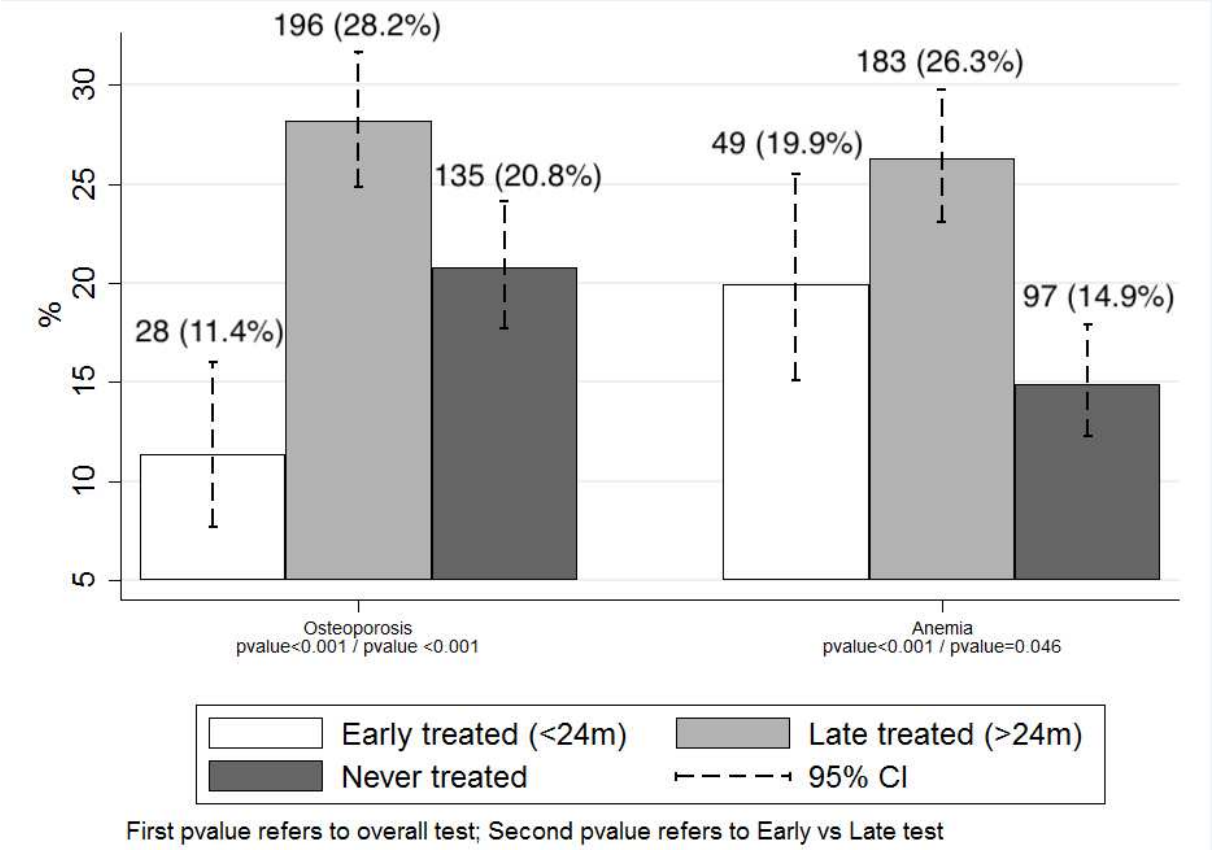


Figure 2: Kaplan–Meier curves showing freedom from developing new bowel stenosis in patients treated early with anti- TNF agents compared to patients treated late with anti-TNF agents, with or without history of previous bowel stenosis



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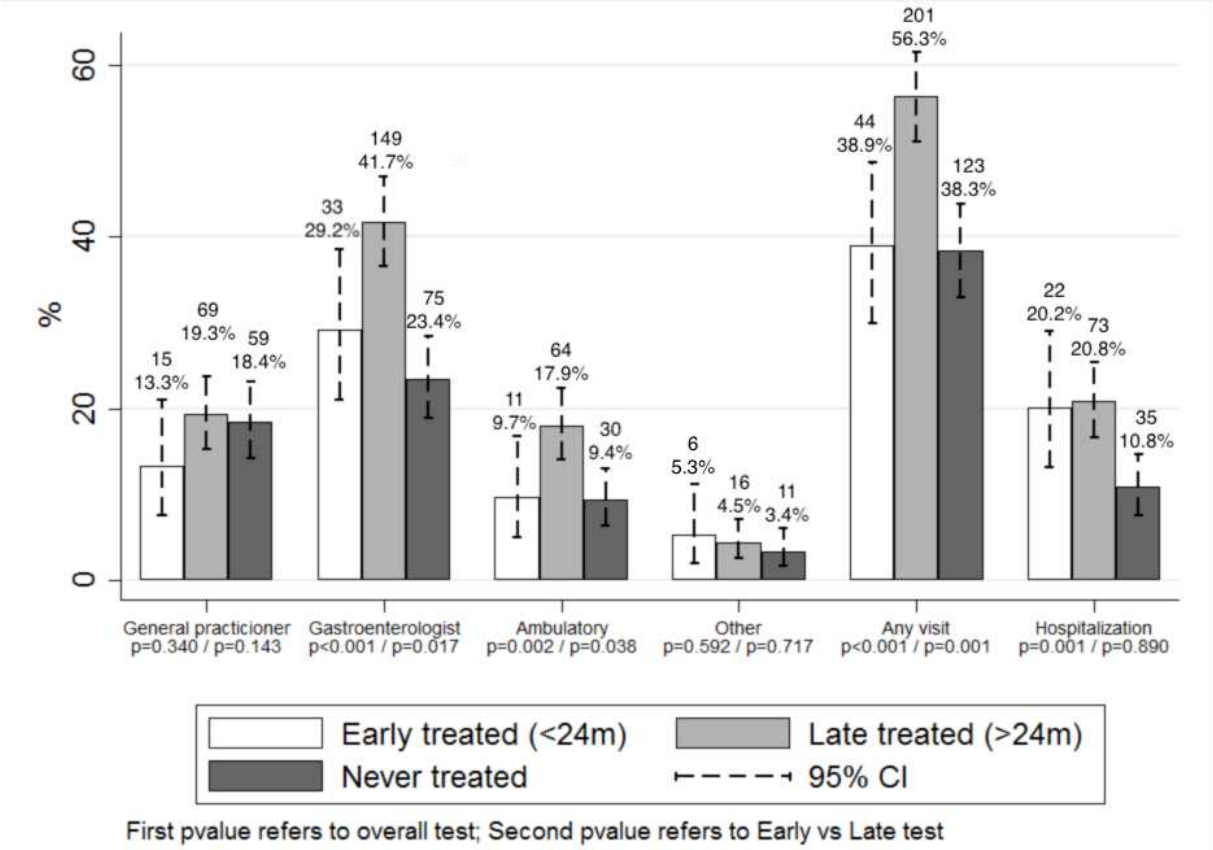
622 Figure 3: Frequency of osteoporosis and anaemia among the different treatment groups.
623 CI: confidence interval
624



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626 Figure 4: Frequency of patients with medical visits and hospitalizations related to IBD
627 among the different treatment groups
628 CI: confidence interval

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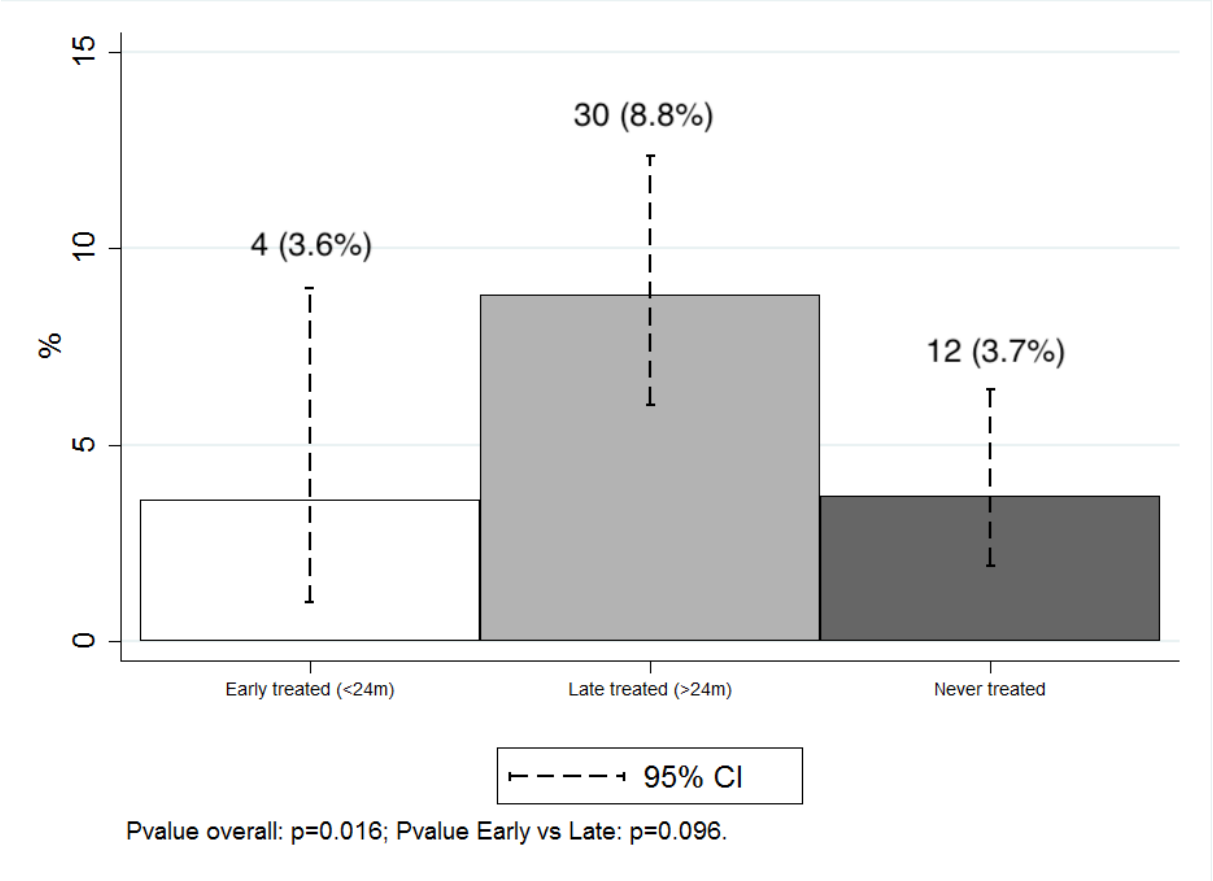

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631 Figure 5: Percentages of patients with absence from work among the three different
632 treatment groups
633 CI: confidence interval

634

635 ***Tables***

636

Anti-TNF treatment:	Early treated (< 24months)	Late treated (>= 24months)	Never treated	P-value global	P-value early vs. late
Number of patients	**246**	**696**	**650**		
Gender					
Male	124 (50.4)	323 (46.4)	309 (47.5)		
Female	122 (49.6)	373 (53.6)	341 (52.5)	0.558	0.280
Age at diagnosis (years) (median, IQR, range)	27, 20-38 13-78	24, 19-32 3-75	29, 22-41 1-81	<0.001	<0.001
Age (years) (median, IQR, range)	32, 26-42 17-88	44, 34-53 19-85	48, 36-62 18-89	<0.001	<0.001
Disease duration (years) (median, IQR, range)	5, 3-7 0-16	16, 11-23 3-47	13, 6-23 0-57	<0.001	<0.001
Months since last reported flare (median, IQR, range)	12, 4-30 0-60	20, 8-36 0-74	16, 6-38 0-77	0.041	0.011
CDAI score at Last Follow-up (median, IQR, range)	25, 6-54 0-280	26, 6-60 0-339	20, 6-46 0-345	0.001	0.247
Behaviour					
B1	94 (38.2)	185 (26.6)	325 (50.0)		
B1p	64 (26.0)	96 (13.8)	69 (10.6)		
B2	42 (17.1)	152 (21.8)	123 (18.9)		
B2p	9 (3.7)	121 (17.4)	64 (9.9)		
B3	17 (6.9)	46 (6.6)	42 (6.5)		
B3p	20 (8.1)	96 (13.8)	27 (4.2)	<0.001	<0.001
Smoking status at diagnosis					
Non-Smoker	134 (54.5)	325 (46.7)	325 (50.0)		
Smoker	102 (41.5)	337 (48.4)	302 (45.5)		
Unknown	10 (4.0)	34 (4.9)	23 (4.5)	0.222	0.111
Smoking status at latest follow-up					
Non-Smoker	163 (66.3)	455 (65.4)	462 (71.1)		
Smoker	81 (32.9)	238 (34.2)	181 (27.9)		
Unknown	2 (0.8)	3 (0.4)	7 (1.1)	0.071	0.694
BMI (median, IQR, range)	23.0, 20.2-25.6 14.6-50.1	22.9, 20.5-26.0 14.7-45.4	23.1, 20.7-26.0 13.9-48.1	0.307	0.794

637 Table 1: Baseline characteristics and demographic data of study population.
638 IQR: interquartile range
639

640

641

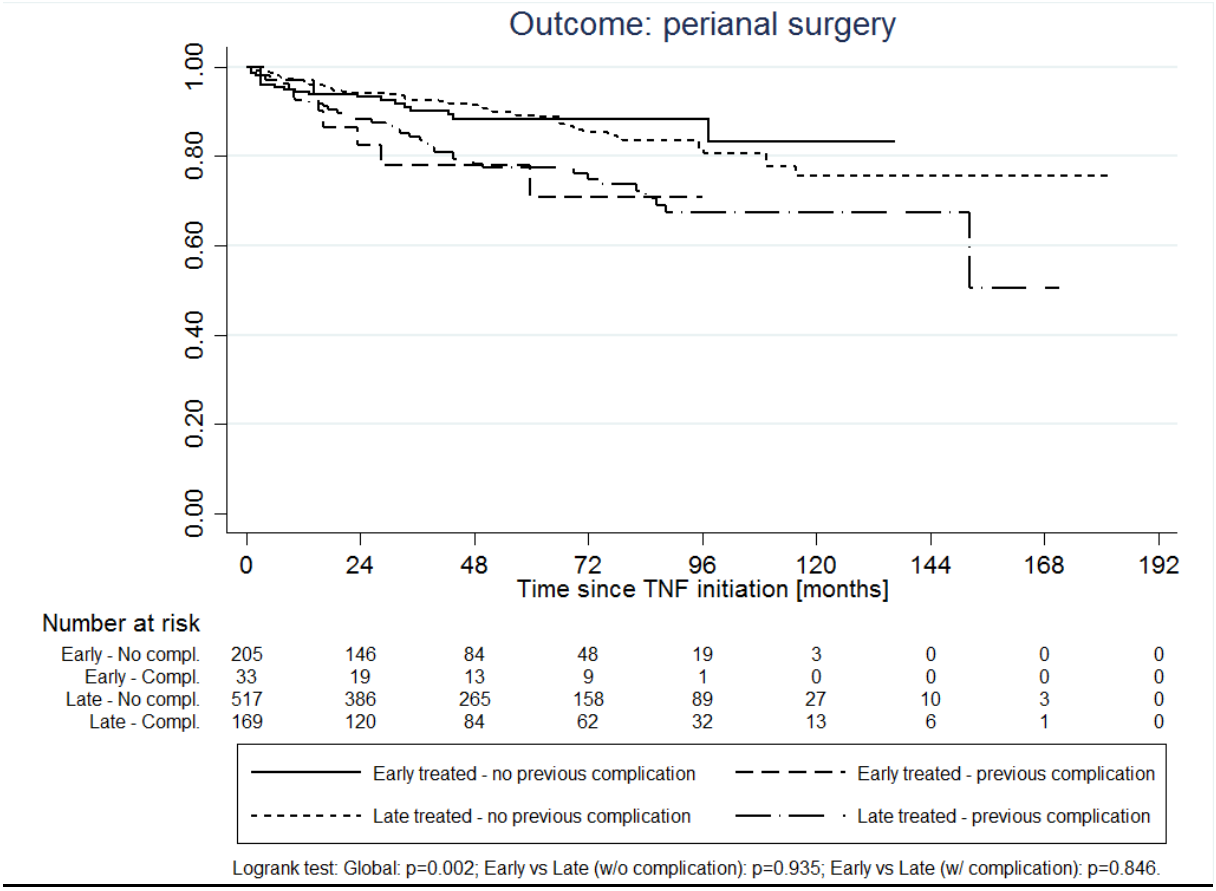
Primary Outcome	Comparison Early – no pre-existing c. vs Early – pre-existing c. vs Late – no pre-existing c. vs Late – pre-existing c. (global test)	Comparison Early vs Late no pre-existing complication	Comparison Early vs Late pre-existing complication
Stenosis	<0.001	<0.001	0.147
Perianal fistula	0.506	0.671	0.560
Other fistula	0.961	0.781	0.676
Any fistula	0.627	0.413	0.519
Perianal surgery	0.002	0.935	0.846
Intestinal surgery	0.623	0.213	0.607
Any surgery	0.927	0.702	0.892
EIM	<0.001	0.750	0.087

642 Table 2: P-values of primary outcomes using Log-rank tests and Kaplan-Meier analysis

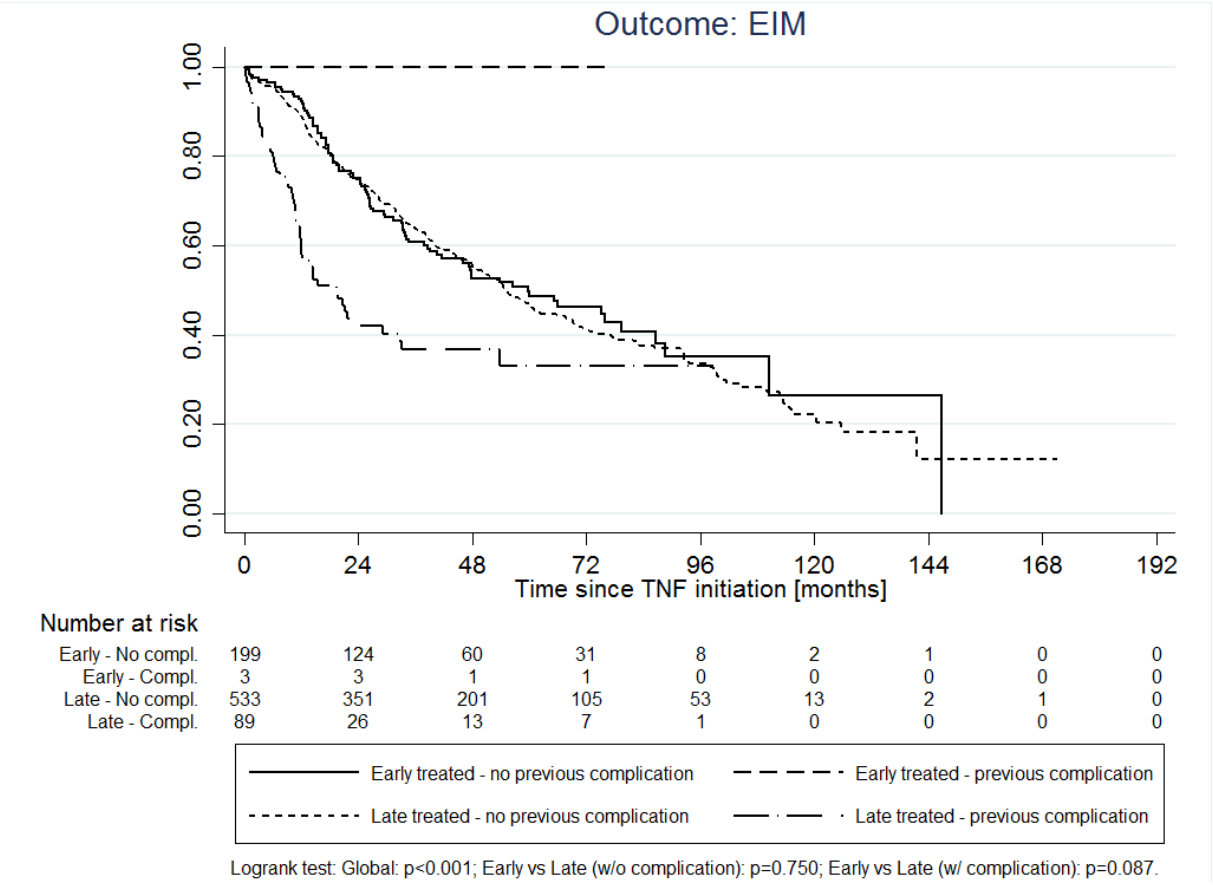
643

Online Supplementary Figures and Tables

Supplementary Figures



Supplementary Figure 1: Kaplan–Meier curves showing no benefit in the need of new perianal surgery in patients treated early with anti- TNF agents compared to patients treated late, with or without history of previous perianal surgeries



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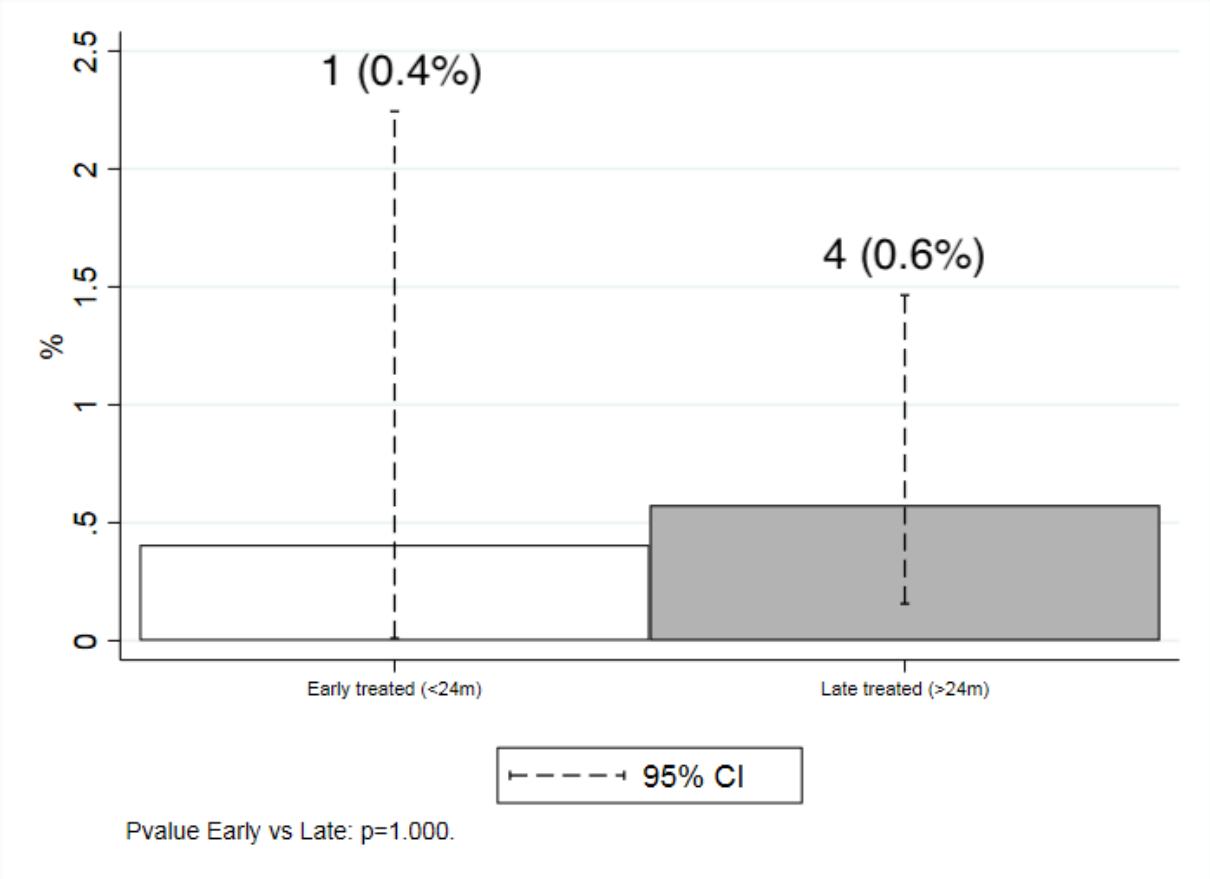
655 Supplementary Figure 2: Kaplan–Meier curves showing no differences in development of
656 EIM in patients treated early with anti- TNF agents compared to patients treated late with
657 anti- TNF agents, with or without history of pre-existing EIM
658



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660 Supplementary Figure 3: Percentages of opportunistic infections which led to anti-TNF
661 therapy cessation between early and late treatment groups
662 CI: confidence interval
663

Supplementary Tables

Primary outcome Parameters	Comparison (logrank test) Early vs Late
Perianal fistula	0.524
Other fistula	0.742
Any fistula	0.331
Bowel Stenosis	<0.001
Intestinal surgery	0.201
Fistula/Abscess surgery	0.698
Any surgery	0.694
EIM	0.208

Supplementary Table 1: P-values of primary outcomes without considering pre-existing complications

95% confidence intervals	Early treated - no pre-existing complication	Early treated - pre-existing complication	Late treated - no pre-existing complication	Early treated - pre-existing complication
Outcome: Stenosis				
2 years	95.1 (90.8-97.4)	100.0 (n/a)	88.1 (84.9-90.7)	83.3 (72.3-90.2)
5 years	83.6 (76.1-89.0)	100.0 (n/a)	68.2 (63.3-72.6)	68.4 (54.1-79.1)
10 years	67.8 (39.0-81.9)	n/a	45.7 (38.9-52.2)	n/a
Outcome: Any Fistula				
2 years	83.8 (77.6-88.4)	100.0 (n/a)	84.5 (81.1-87.4)	69.8 (54.1-81.1)
5 years	70.4 (62.4-77.1)	100.0 (n/a)	69.1 (64.4-73.3)	65.5 (48.2-78.2)
10 years	60.1 (46.7-71.2)	n/a	50.7 (43.7-57.3)	n/a
Outcome: Perianal Fistula				
2 years	90.0 (84.7-93.5)	100.0 (n/a)	89.0 (86.0-91.4)	70.8 (53.2-82.8)
5 years	77.0 (69.4-83.0)	100.0 (n/a)	76.6 (72.3-80.4)	70.8 (53.2-82.8)
10 years	68.2 (55.0-78.3)	n/a	63.6 (56.8-69.7)	n/a
Outcome: Any surgery				
2 years	87.2 (81.2-91.4)	83.2 (67.8-91.6)	86.4 (81.9-89.8)	88.0 (83.9-91.1)
5 years	76.3 (68.0-82.7)	68.7 (49.4-81.9)	75.6 (69.6-80.6)	75.0 (69.3-79.8)
10 years	70.8 (56.5-81.2)	n/a	57.2 (45.5-67.3)	60.6 (52.9-67.5)
Outcome: Perianal surgery				
2 years	93.2 (88.6-96.0)	82.5 (62.6-92.4)	94.0 (91.4-95.8)	88.3 (82.1-92.5)
5 years	88.3 (82.0-92.5)	70.8 (46.3-85.7)	89.2 (85.5-91.9)	77.4 (69.2-83.6)
10 years	83.4 (69.5-91.3)	n/a	75.6 (67.2-82.2)	67.4 (57.0-75.8)
Outcome: EIM				
2 years	75.0 (68.1-80.7)	100.0 (n/a)	74.7 (70.7-78.3)	42.0 (30.8-52.7)
5 years	49.8 (41.4-57.6)	100.0 (n/a)	46.8 (41.8-51.5)	33.1 (21.4-45.3)
10 years	26.3 (11.5-44.0)	n/a	22.1 (15.9-29.0)	n/a

Supplementary Table 2: Percentage of patients with 95% confidence intervals free from the indicated complication at specific time points

Anti-TNF treatment:	Early treated (< 24months)	Late treated (>= 24months)	Never treated	P-value global	P-value early vs late
Osteoporosis	28 (11.4)	196 (28.2)	135 (20.8)	<0.001	<0.001
Anaemia	49 (19.9)	183 (26.3)	97 (14.9)	<0.001	0.046

672 Supplementary Table 3: Rates and differences of osteoporosis and anaemia between
673 treatment groups
674

Anti-TNF treatment:	Early treated (< 24months)	Late treated (>= 24months)	Never treated	P-value global	P-value early vs late
Medical visits in last 3 months (related to IBD)					
General practitioner	15 (13.3)	69 (19.3)	59 (18.4)	0.340	0.143
Gastroenterologist	33 (29.2)	149 (41.7)	75 (23.4)	<0.001	0.017
Ambulatory (outpatient)	11 (9.7)	64 (17.9)	30 (9.4)	0.002	0.038
Other visit	6 (5.3)	16 (4.5)	11 (3.4)	0.592	0.717
Any of the above	44 (38.9)	201 (56.3)	123 (38.3)	<0.001	0.001
Hospitalization in last 3 months					
No	87 (79.8)	278 (79.2)	288 (89.2)		
Yes	22 (20.2)	73 (20.8)	35 (10.8)	0.001	0.890

675 Supplementary Table 4: Medical visits and hospitalizations during the last 3 months
676

Anti-TNF treatment:	Early treated (< 24months)	Late treated (>= 24months)	Never treated	Pvalue global	Pvalue early vs late
Work disability during last 3 months					
No	107 (96.4)	310 (91.2)	311 (96.3)		
Yes	4 (3.6)	30 (8.8)	12 (3.7)	0.016	0.096

677 Supplementary Table 5: Absence from work of CD patients during the last 3 months
678

Anti-TNF treatment:	Early treated (< 24months)	Late treated (>= 24months)	Never treated	P-value global	P-value early vs late
Colorectal cancer (CRC)	3 (1.2)	2 (0.3)	5 (0.8)	0.184	0.115
Intestinal lymphoma (IL)	2 (0.8)	4 (0.6)	1 (0.2)	0.244	0.654

679 Supplementary Table 6: Rates and differences of CRC and IL between treatment groups